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The EPIC-InterAct Study

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Replacement of red and processed meat with other food sources of protein and the risk of type 2 diabetes in European populations; the EPIC-InterAct study

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Abstract

OBJECTIVE

There is sparse evidence for suitable food substitutions for red and processed meat on risk of type 2 diabetes. We modelled the association between replacing red and processed meat with other protein sources and the risk of type 2 diabetes and estimated its population impact.

RESEARCH DESIGN AND METHODS

The European Prospective Investigation into Cancer (EPIC)-InterAct case-cohort included 11,741 type 2 diabetes cases and a subcohort of 15,450 participants in eight countries. We modelled the replacement of self-reported red and processed meat with poultry, fish, eggs, legumes, cheese, cereals, yogurt, milk and nuts. Country-specific hazard ratios (HR) for incident type 2 diabetes were estimated by Prentice-weighted Cox regression and pooled using random-effects meta-analysis.

RESULTS

There was a lower hazard for type 2 diabetes for the modelled replacement of red and processed meat (50 g/day) with cheese (HR 0.90, 95% confidence interval 0.83–0.97; 30 g/day), yogurt (0.90, 0.86–0.95; 70 g/day), nuts (0.90, 0.84–0.96; 10 g/day) or cereals (0.92, 0.88–0.96; 30 g/day) but null for replacements with poultry, fish, eggs, legumes or milk.

Assuming a causal association, replacing red and processed meat with cheese, yogurt or nuts could prevent 8.8%, 8.3% or 7.5%, respectively, of new cases of type 2 diabetes.

CONCLUSIONS

Replacement of red and processed meat with cheese, yogurt, nuts or cereals was associated with a lower rate of type 2 diabetes. Substituting red and processed meat by other protein sources may contribute to the prevention of incident type 2 diabetes in European populations.

Type 2 diabetes is a major public health challenge and its prevalence is projected to increase from 463 million in 2019 to 700 million by 2045 (1). One key modifiable risk factor in the prevention of type 2 diabetes is diet (2). Most dietary recommendations to prevent type 2 diabetes advise that intake of red and processed meat should be limited, mainly based on evidence from cohort studies (3–5), including the multi-country European Prospective Investigation into Cancer (EPIC)-InterAct study (6). However, few studies have quantified the risk associated with replacement of red and processed meat by other food sources of protein (5). Other food sources of protein in European diets include poultry, fish, cheese, yogurt, milk, eggs, legumes, nuts and cereals (7). A previous study reported that replacing red and processed red meat with poultry, low-fat dairy, whole grains or nuts was associated with a lower risk of type 2 diabetes in three US cohorts of health professionals (8). This study did not investigate different types of dairy products (cheese, yogurt, milk), eggs or legumes.

We aimed to investigate the impact of replacing red and processed meat with other food sources of protein (poultry, fish, cheese, yogurt, milk, eggs, legumes, nuts and cereals) on the development of type 2 diabetes. Moreover, we estimated the population attributable fraction for replacements associated with lower rates of type 2 diabetes. Lastly, based on previous findings (9,10), we estimated the contribution of iron storage (serum ferritin) as a potential mediator.

RESEARCH DESIGN AND METHODS

The EPIC-InterAct Study

Study population

EPIC-InterAct is a case-cohort study nested within the EPIC cohort (11). A detailed description of the study design can be found elsewhere (12). In brief, the EPIC-InterAct study identified type 2 diabetes cases among study participants from eight countries (France, Italy,

Spain, the United Kingdom, the Netherlands, Germany, Sweden and Denmark) included in EPIC with available blood samples (n=340,234; 3.99 million person-years of follow-up from 1991-2007). After excluding prevalent cases of type 2 diabetes at baseline (n=548), the study included 12,403 verified cases of incident type 2 diabetes and 16,154 participants in a representative subcohort, including, by design, an overlap of 778 incident type 2 diabetes cases. After we excluded participants in the bottom and top 1% of the energy intake/requirement ratio (n=619) and those with missing information on dietary data (n=736), education (n=330), physical activity (n=385) and BMI (n=197), a total of 15,450 participants in the subcohort and 11,741 type 2 diabetes cases were included in this analysis (Supplemental Fig. S1). All participants gave written informed consent and the study was approved by the local ethics committees in the participating countries and the Internal Review Board of the International Agency for Research on Cancer.

Dietary assessment

Habitual dietary intake for the 12 months before entering the study was assessed using self- or interviewer-administered country-specific food frequency questionnaires (FFQs) or diet history interviews (11,13). Further information on dietary assessments methods and correlation coefficients for protein and food sources of protein from validation studies are in Supplemental Table S1. The questionnaires were used to estimate the average daily intake of foods and nutrients. A single 24h dietary recall was collected from an 8% random sample of participants from each country.

We considered the following food sources of protein: red meat, processed meat, poultry, fish, cheese, yogurt, milk, eggs, nuts, legumes and cereals. Cereal consumption was included as this food group was the largest non-animal food source of protein in EPIC (7). Definition of individual foods groups are in Supplemental Table S2.

Portion sizes were designated as 200 g/day for milk, 70 g/day for yogurt, 50 g/day for red and processed meat, poultry, fish, eggs and legumes, 30 g/day for cheese and cereals and 10 g/day for nuts, all based on previously reported serving sizes or intake ranges from the EPIC-InterAct study (6,14–16). As information on servings was not available for legumes and cereals, we used those in recent meta-analyses (17,18).

Type 2 diabetes ascertainment

Multiple sources of information from each EPIC study centre were used to ascertain type 2 diabetes cases including self-report, linkage to primary-care, secondary-care, drug, hospital admissions and mortality data as described previously (12). Cases identified from only one independent source were verified through at least one other source, including medical records. Because cases in Denmark and Sweden were ascertained using local and national diabetes registers these cases were considered verified. Follow-up was censored at the date of diagnosis, loss to follow-up, death or 31 December 2007, whichever came first.

Covariate assessment

Data on lifestyle and medical history were obtained from self-administered questionnaires at baseline including education, physical activity, smoking and alcohol. Physical activity was classified according to the Cambridge Physical Activity Index. Validity of the index was assessed against objectively measured energy expenditure (19). Height, weight and waist circumference were measured by trained personnel using standardised protocols during a clinic visit at baseline in all study centres, except Oxford (UK) and centres in France which obtained self-reported measures. Waist circumference was not available in Umeå (Sweden). Body mass index (BMI) was calculated as weight (kilograms) divided by height (meters) squared. History of prevalent cancer, myocardial infarction, stroke, angina, hypertension or hyperlipidemia was based on self-report.

At the baseline, clinic visit blood samples were collected and stored at -196°C (-150°C in Denmark and -80°C in Sweden) at the co-ordinating centre or local biorepositories. Serum (except for plasma in Umeå) ferritin, as a marker of body iron storage, was analysed at SHL-Groep, Etten-Leur, the Netherlands, using Cobas (Roche Diagnostics, Mannheim, Germany) assays (electrochemiluminescence immunoassay sandwich principle) on a Roche Hitachi Modular P analyser. The assay range was 0.5-2000 µg/L. Cobas assays were also used to measure high-sensitive C-reactive protein (hs-CRP) (20).

Statistical analysis

Standard descriptive statistics were used to summarize baseline characteristics for the total subcohort and incident type 2 diabetes. We have previously reported the baseline characteristics of the study population across quintiles of meat intake in the subcohort (6).

The modelled associations of replacing red meat with the other protein sources were estimated with Prentice-weighted Cox regression models. The models were fitted separately by country and were used to estimate hazard ratios (HR) and 95% confidence intervals (CI) for the replacement of red and processed meat by other food sources of protein. Then, country-specific estimates were pooled using random-effects meta-analysis and between country-heterogeneity was quantified using the I^2 statistic.

We adjusted for a range of covariates in a series of models. Model 1 included age (timescale), study centre (2 to 6 centres in each country), energy intake (kcal/day; continuous), sex (stratified by baseline hazard function), education (none, primary school, secondary school, longer incl. university), physical activity (inactive, moderate inactive, moderately active, active), smoking status (never, former, current, unknown) and alcohol intake (g/day; two continuous terms for a non-linear relationship based on three-knots restricted cubic spline function). In model 2 we further adjusted for dietary variables including fruit, vegetables (excl. legumes), sweets, soft drinks, coffee, tea and intake of other

dairy products (e.g. cream desserts and dairy creams) (all in g/day; continuous). In model 3 (specified as the main model) we further adjusted for BMI (kg/m^2 ; continuous). In a further model we also adjusted for self-reported history of hypertension (yes, no, unknown), self-reported history of dyslipidaemia (yes, no, unknown) and waist circumference (cm; continuous).

The modelled association of each food replacement was estimated as follows using multivariable-adjusted regression. We first obtained regression coefficients (i.e. log hazard ratios) per one serving/day for red and processed meat and each of the other food sources of protein (i.e. poultry, fish, cheese, yogurt, milk, eggs, legumes, nuts and cereals). Then, we calculated the difference between the two coefficients, accounting for their variance and covariance, and exponentiated the difference to estimate the hazard ratio for each specific replacement of interest (21). Analyses were also performed excluding participants who consumed $<10\text{g/day}$ of red and processed meat. Additionally, replacements of red meat and processed meat were evaluated separately.

To investigate sources of heterogeneity between countries, we performed separate analyses in Northern and Southern Europe. We were not able to differentiate between intake of refined and whole grains, therefore in an exploratory analysis we stratified the replacement of red and processed meat with cereals by high and low intake of dietary fibre from cereals divided at the median of the subcohort, i.e. 8 g/day . Based on previous findings (6), we also stratified the replacement of red and processed meat with poultry analysis by sex.

One of the mechanisms by which a high intake of red and processed meat may be associated with development of type 2 diabetes is through its high content of haem iron (22). We compared substitution models with and without adjustment for ferritin, a marker of body iron storage, using a one-sided Wald-test (23), separately for model 2 and 3 (without and with adjustment for BMI, respectively) among those with measured ferritin levels. Because ferritin

is an acute-phase reactant and could therefore be elevated due to systemic inflammation, we additionally adjusted model 3 for hs-CRP, a marker of systemic inflammation (24). To quantify the extent to which ferritin explained the lower incidence rate arising from each replacement, we calculated: $[\text{HR}_{\text{replacement not adjusted}} - \text{HR}_{\text{replacement adjusted for ferritin}}] / [\text{HR}_{\text{replacement not adjusted}} - 1]$. A bootstrapping procedure (1000 replicates) was used to derive 95% confidence intervals.

In sensitivity analyses, we 1) excluded participants with cancer, myocardial infarction, stroke, angina, self-reported hypertension and/or hyperlipidaemia at baseline, 2) excluded cases that occurred during the first two years of observation, due to concerns about reverse causation, 3) excluded individuals with HbA_{1c} levels $\geq 6.5\%$ (equivalent to 48 mmol/mol) measured at the baseline visit, 4) applied regression calibration to all dietary intakes due to possible measurement error in self-reported dietary intakes. We regressed intakes from the 24-h dietary recalls on those from the FFQs in a multivariable-adjusted linear mixed model with country as a random effect. The HRs were then corrected by dividing the log HRs by the regression dilution ratio. Uncertainty in the calibration model was accounted for by sampling a set of five values using a multiple imputation approach. Corrected log HRs and standard errors were calculated and pooled using Rubin's rules (25). 5) We also estimated replacements per 5 g protein from each source of protein.

We estimated the population attributable fraction for the modelled replacements associated with a lower hazard of type 2 diabetes in the subcohort, under the assumption of causality, to investigate how much of the incidence of type 2 diabetes could be preventable by replacing red and processed meat with another protein source. The population attributable fraction was calculated as the difference between the predicted incidence rate (IR) for the overall subcohort and the predicted IR for the relevant replacements divided by the overall incidence rate (i.e. $[\text{IR}_{\text{subcohort}} - \text{IR}_{\text{replacement}}] / [\text{IR}_{\text{subcohort}}]$). All IRs were adjusted for model 3 covariates

and 95% CIs were derived using a bootstrap procedure with 1000 replications. All analyses were performed in Stata 15.1 (StataCorp, College Station, TX, USA).

RESULTS

The median follow-up time was 12.3 years. Table 1 shows the baseline characteristics of the subcohort and cases of type 2 diabetes. Type 2 diabetes cases were older, more likely to be men, have a lower education level, be physically inactive, smoke, and have a higher BMI and higher levels of serum ferritin compared with subcohort participants. Those with type 2 diabetes had a slightly higher intake of red and processed meat and soft drinks and a lower intake of yogurt, sweets and fruits.

Modelled replacement of red and processed meat with cheese, yogurt, nuts or cereals was associated with lower hazard of type 2 diabetes (Fig. 1 and Supplemental Fig. S2). Replacing red and processed meat with fish also suggested a lower rate of type 2 diabetes (HR 0.91, 95% CI 0.84–1.00; $p=0.046$) and a similar point estimate was observed for poultry, but with wider CIs (0.91, 0.77–1.07). Replacing red and processed meat with milk, eggs or legumes was not significantly associated with type 2 diabetes risk. Additional adjustment for BMI attenuated most of the associations with type 2 diabetes, particularly the replacement of red and processed meat with legumes (model 2: 0.88, 0.80–0.96 and model 3: 1.01, 0.86–1.19). Similar patterns of associations as in the main analysis were observed after excluding very low consumers of red and processed meat ($n=739$) (data not shown) and when red meat and processed meat were replaced separately (Supplemental Fig. S3). Replacing processed meat with fish was associated with a lower hazard of type 2 diabetes (0.82, 0.71–0.94), whereas replacing red meat with fish was not (0.95, 0.86–1.04).

There was heterogeneity between countries for the replacement of red and processed meat with poultry or fish (Supplemental Fig. S2). This was not explained by European region (i.e.

north and south Europe) (Supplemental Fig. S4). Stratification by sex for the replacement of red and processed meat with poultry showed associations in different directions for men and women: poultry (men: 0.74, 0.59–0.93; women 1.16, 0.89–1.52; p for interaction 0.04). After stratification of the replacement of red and processed meat with cereals by high or low cereal fibre, we found no substantial differences between strata (Supplemental Fig. S5).

Adjustment for ferritin attenuated the estimated HRs for all replacement analyses, with and without adjustment for BMI (Supplemental Table S3). Further adjusting for hs-CRP did not change the results (data not shown). 22.1 to 31.8% of the lower incidence rate observed for replacement of red and processed meat with cheese, yogurt, nuts and cereals was explained by serum ferritin (Fig. 3).

Across all sensitivity analyses a similar pattern of associations was observed as in the main analysis (Supplemental Fig. S6) except for replacement with 5 g protein/day from cereals, which was not associated with diabetes risk (0.99, 0.94–1.04) (Supplemental Fig. S7). The population attributable fraction for the modelled replacement of one serving/day of red and processed meat with one serving/day of cheese, yogurt or nuts was 7.5% to 8.8% of type 2 diabetes cases in our study (Table 2). For cereals, the confidence interval was wide and included zero.

CONCLUSIONS

In this large case-cohort study across eight European countries, we used substitution modelling and estimated that replacing red and processed meat with cheese, yogurt, nuts or cereals was significantly associated with a lower rate of type 2 diabetes whereas replacing red and processed meat with poultry, fish, milk, eggs or legumes was not. Mediation analysis suggested that these associations were partially mediated by body iron storage as assessed by serum ferritin levels. Assuming causality, 7.5 to 8.8% of the observed cases of type 2

diabetes could have been prevented if all participants replaced one serving/day of red and processed meat with one serving/day of cheese, yogurt or nuts.

This prospective case-cohort study included individuals from geographically diverse populations across Europe. By specifying modelled food substitutions, the results allow a clear interpretation for public health and healthful selection of other protein sources as alternatives to red and processed meat for the primary prevention of type 2 diabetes. The serving sizes in g/day were based on previous literature and study intake ranges. The difference in energy content between the substituted foods may leave an unspecified energy substitution (for instance, the energy difference between 50 g of red meat and 30 g of cheese) that must be compensated for by other foods not in the model. However, serving size information in g/day is likely to be more readily understood than information in units of energy percent or kcal/day. All replacements may not be applicable to a single meal-setting but rather to longer-term average replacements in the habitual diet. For instance, replacing 50 g of red meat with 10 g of nuts in a single meal may not be realistic. Dietary intake information was obtained from cohort-specific semi-quantitative FFQs or diet history interviews across eight different European countries. This provided greater variation in intakes than in studies that included participants from a single country. Still, intake of nuts was generally low which highlights the importance of a cautious interpretation.

A limitation of the current study is that the food substitutions were inferred based on a statistical model that compared individuals with different average intakes while no one actively changed their diet. Conducting randomized controlled trials of foods for long-term health endpoints such as type 2 diabetes is not practical, and in their absence well conducted prospective studies that not only assess associations of food intake but model food substitutions can be helpful. We also acknowledge the limitation of our use of a single measure of diet and covariates and we were not able to examine changes over time.

Nevertheless, our results are consistent with those from studies modelling repeated measures of red and processed meat intake as either average intake or dietary changes (8,26). Self-reported dietary measures are prone to error. While we observed similar patterns of associations after regression calibration against a single 24-hour recall, errors due to self-reporting, covariate measurement errors and confounding due to unmeasured factors may bias our findings in either direction. Type 2 diabetes cases were verified in our study and the risk of misclassification was low. Analysis excluding undiagnosed diabetes at baseline showed similar patterns of associations.

There is limited evidence from prospective studies about the effects of replacing red and processed meat with other protein sources on incident type 2 diabetes. Pan *et al.* found that replacing red and processed red meat with nuts, low-fat dairy, whole grain, poultry and fish was associated with a lower risk of type 2 diabetes (8). We found that the HRs for replacing red and processed meat with fish or poultry were similar in magnitude to the estimates for cheese, yogurt, nuts and cereals but with wider CIs and not statistically significant. When replacing processed meat with fish, but not when replacing unprocessed red meat with fish we observed a lower rate of type 2 diabetes. Also, we found that replacing red and processed meat with poultry was associated with a lower diabetes rate in men, but not in women. The reasons for these differences by sex are unclear, but we may speculate that differences in preparation methods and types of red and processed meat as well as poultry and fish consumed by men and women in different countries may contribute, though we were unable to test this in our study. We found that replacing red and processed meat with fermented dairy products, such as yogurt and cheese, but not with milk, was associated with a lower rate of type 2 diabetes. Neither prior reports from US-based cohorts (8) nor our current study are able to clarify whether the type of dairy product (such as fermented or not) or specifically its nutrient content is more important for type 2 diabetes risk.

To our knowledge, no previous study has investigated the association of replacing red and processed meat with eggs or legumes on the development of type 2 diabetes. Other cohort studies, that have not specified food substitutions, have suggested that intake of eggs was not associated with risk of type 2 diabetes in Europe or Asia, but positively associated with risk in the US, with significant heterogeneity by region (27). Legume intake was not associated with type 2 diabetes in a recent umbrella review of meta-analyses (5), although the definitions of legumes varied substantially across studies, which is also the case across our study centres. Overall, due to the low intake of legumes in some countries, most estimates were, however, imprecise and further research is needed.

There is consistent evidence from cohort studies linking whole grains to a lower risk of type 2 diabetes (18), but in the current study we were not able to differentiate between the intake of refined and whole grains. In an exploratory analysis stratifying the study population by cereal fibre, we found no substantial differences between strata. This could be a reflection of the absence of an association between refined grain and type 2 diabetes in this study, as in some other populations (18). When replacing 5 g protein from red and processed meat with 5 g protein from cereals we found no association, suggesting that other nutrients in cereals, like dietary fibre, may drive the observed association. Our results extend the previous findings in the US study to a European population and highlight that some, but not all, food sources of protein may be beneficial for type 2 diabetes risk as alternatives to red and processed meat. A caveat to this is that the point estimates for poultry and fish were similar to the other replacement foods', but with less precision.

In this study, we were able to investigate whether body iron stores, measured as serum ferritin, could mediate the association of replacing red meat with other sources of protein. Our results suggest that ferritin may explain up to 31.8% of the observed associations, although the associations were, in general, weak. This is in line with a previous finding that

serum ferritin may partly mediate the association between intake of red meat and risk of type 2 diabetes in the EPIC-Potsdam study (9). There are, however, alternative explanations for the potential benefits of substituting red meat with other protein sources. BMI could be regarded as a mediator. We found that most of our estimates were attenuated after adjustment for BMI as was also observed in a large Chinese cohort (28), and higher consumption of red and processed meat has also been associated with weight gain in the EPIC study (29). We only had a single measure of BMI and could not study weight change, but we pre-specified including baseline BMI as a potential confounder. Advanced glycation end products formed during the preparation of red and processed meat may increase body weight, inflammation and insulin resistance (30,31). Nitrates and nitrites, which are commonly found in processed meat, can be converted to nitrosamines which have been linked with insulin resistance and may be toxic to pancreatic beta-cells (30). Negative effects from preparation methods of other meat products, such as poultry or fish, might explain why these replacements were not associated with a lower risk of type 2 diabetes. Fermented dairy products like cheese and yogurt contain odd-chain fatty acids, ruminant trans fatty acids and probiotic bacteria, all of which have been hypothesised to have beneficial effects on glucose metabolism (32,33). Cereals, in our study consisting of both refined and whole grains, may lower the diabetes risk primarily through the intake of whole grains high in dietary fibre and phytochemicals with benefits on the production of short-chain fatty acids, improved insulin sensitivity and glucose control and anti-inflammatory effects (34).

Under the assumption of causal effects, stable dietary intakes and linear incidence rates, our estimate of the population attributable fraction suggested that 7.5% (95% CI 3.3% to 11.3%) to 8.8% (3.1% to 13.6%) of observed type 2 diabetes cases could have been prevented if the population had replaced one serving/day of red and processed meat with one serving/day of cheese, yogurt or nuts. This is relevant for public health. Our study paid close

attention to accounting for a range of potential confounding factors and addressed a number of potential biases. Our study was undertaken in meat consuming European populations and the results cannot, therefore, necessarily be generalised to non-European populations with different dietary habits. Although studies suggest that red and processed meat intake is positively associated with the development of type 2 diabetes (6), this may also depend on the consumption levels of other foods consumed in the diet, such as fibre- or calcium-rich foods, and whether or not red and processed meats are consumed within an overall healthy diet (35).

In conclusion, this study suggests that the replacement habitually of one serving/day of red and processed meat with one serving/day of cheese, yogurt, nuts or cereals may be associated with a lower rate of development of type 2 diabetes. Replacing red and processed meat with other sources of protein may have public health impact for the prevention of type 2 diabetes.

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Tables

Table 1–Baseline characteristics of the EPIC-InterAct case-cohort study (n=26,460)

	Total subcohort (n=15,450)	Type 2 diabetes cases (n=11,741)
Characteristics	Median (IQR)	Median (IQR)
Age, years	53 (47-59)	56 (50-61)
Women, %	62	50
Lower education, %	41	51
Physically inactive, %	24	30
Smoker, %	26	28
Body mass index, kg/m ²	26 (23-28)	29 (26-32)
<i>Foods</i>		
Red and processed meat, g/day	74 (46-108)	84 (53-121)
Red meat, g/day	38 (19-65)	43 (23-71)
Processed meat, g/day	28 (15-49)	32 (17-56)
Poultry, g/day	16 (7-31)	16 (7-32)
Fish, g/day	29 (15-52)	32 (16-55)
Cheese, g/day	28 (14-51)	26 (12-49)
Yogurt, g/day	26 (0-97)	20 (0-88)
Milk, g/day	165 (45-301)	170 (47-321)
Eggs, g/day	15 (7-25)	16 (7-28)
Legumes, g/day	5 (0-23)	4 (0-20)
Nuts, g/day	1 (0-3)	0 (0-2)
Cereals, g/day	197 (140-273)	197 (137-273)
Other dairy, g/day	6 (0-24)	5 (0-21)
Sweets, g/day	71 (40-112)	65 (35-110)
Soft drinks, g/day	3 (0-66)	10 (0-92)
Fruit, g/day	193 (103-315)	182 (96-307)
Vegetables (excl. legumes), g/day	155 (101-239)	149 (95-234)
Coffee, g/day	270 (90-525)	287 (90-536)

Tea, <i>g/day</i>	3 (0-197)	0 (0-119)
<i>Nutrients</i>		
Total energy intake, <i>kcal/day</i>	2057 (1679-2515)	2084 (1685-2575)
Alcohol*, <i>g/day</i>	8 (2-20)	8 (2-22)
Alcohol abstainers, %	8	10
Dietary fibre, <i>g/day</i>	22 (17-27)	22 (19-27)
Serum ferritin, $\mu\text{g/l}$	82 (39-156)	132 (65-242)

*Only in consumers, n=14,264 in subcohort and n=10,626 in cases.

Table 2—Population attributable fraction for type 2 diabetes calculated in the subcohort (n total = 15,450) of the InterAct study

Other food sources of protein to replace red and processed meat with*	Population attributable fraction (95% CI)†
Cheese	8.8 % (3.1 to 13.6)
Yogurt	8.3 % (3.3 to 12.7)
Nuts	7.5 % (3.3 to 11.3)
Cereals	17.1 % (-6.7 to 33.3)

*Serving sizes were 200 g/day for milk, 70 g/day for yogurt, 50 g/day for red and processed meat, poultry, fish, eggs and legumes, 30 g/day for cheese and cereals and 10 g/day for nuts. †Confidence intervals (CI) were derived from a bootstrap procedure to the difference between the predicted incidence rate for the overall subcohort and the predicted incidence rate for the relevant replacements divided by the overall incidence rate using 1000 replicates.

Figure legends

Figure 1–The estimated association of replacing red and processed meat (per 50 g/day) with other food sources of protein and the incidence of type 2 diabetes in the EPIC-InterAct case-cohort study (n total = 26,460, n cases = 11,741). Country-specific estimates were obtained and combined using random effects meta-analysis.

Adjusted for: age (underlying timescale), sex, centre, education, physical activity, smoking status, total energy intake, alcohol consumption, fruit, vegetables, sweets, soft drinks, coffee, tea, other dairy products and body mass index.

Figure 2–Estimated % of the association between replacement of red and processed meat with other food sources of protein and risk of type 2 diabetes that is explained by serum ferritin (n total = 24,611, n cases = 10,769). Confidence intervals (CI) were derived from a bootstrap procedure using 1000 replicates. Hazard ratios on which these estimates are based were estimated from Prentice-weighted Cox regression models adjusted for age (underlying timescale), sex, centre, country, education, physical activity, smoking status, total energy intake, alcohol consumption, fruit, vegetables, sweets, soft drinks, coffee, tea, other dairy products and body mass index. Serving sizes were 70 g/day for yogurt, 50 g/day for red and processed meat, 30 g/day for cheese and cereals and 10 g/day for nuts. Estimated % of association explained calculated by: $((HR_{\text{without}} - HR_{\text{with}}) / (HR_{\text{without}} - 1)) * 100$.